[redacted]

P-18-0227

Chemical Name: D-Glucaric acid
CASRN: 87-73-0

ASSIGNMENTS	NAME	DATE
SAR Assessor (A)	**Mitch Sumner**	Hazard Rev Date
HH Tox Assessors (A)	**Doritza Pagan-Rodriguez, Cal Baier-Anderson**	7/18/2018
HH Hazard QC Reviewer (A)	**Jocelyn Hospital**	7/19/2018
Technical Integrator/RA (B)	**Jocelyn Hospital**	7/27/2018
Risk QC Reviewer (B)	**Cal Baier-Anderson**	7/31/2018

Human Health Report Status:		DATE COMPLETED
X	HAZARD DRAFT- Pending Review	7/18/2018
X	HAZARD REVIEWED	7/19/2018
X	HAZARD FINAL	7/19/2018
X	RISK DRAFT- pending review	7/27/2018
X	RISK REVIEWED	8/2/2018
X	RISK-FOCUS FINAL- Uploaded	8/2/2018
	POST-FOCUS UPDATE DRAFT	
	POST-FOCUS UPDATE FINAL- Uploaded	

[redacted]

1 HUMAN HEALTH SUMMARY

1.1 Hazard Summary

- The hazard assessment is based on data on the chemical structure of the PMN, the physical chemical properties (molecular size, water solubility, and estimated hydrophilicity) and information on D-glucaric acid and on the analog tartaric acid (CAS RN 87-69-4 and CASRN 526-83-0). There are no identified structural alerts or available QSAR data.
- Absorption of the neat solid crystalline powder material is expected to be poor through the skin and good through the lung and G.I. based on physicochemical properties. When in aqueous solution, absorption is expected to be moderate through the skin and good through the lung and G.I. properties. The PMN is expected to be highly biodegradable to shorter chain sugars in the human body.
- There is concern for irritation in eye, skin and lung, based on PMN and analog data.
- There is concern for corrosivity for handling glucaric acid in solution, based on PMN and analog data.
- There are no additional identified hazards associated with acute or repeated dosing based on PMN and analog data. The lowest identified effect level was 274 mg/kg bw/day based on no effects at highest dose tested for tartaric acid in an OECD Guideline 414 study (Prenatal Developmental Toxicity Study).

1.2 Risk Summary

1.2.1 Workers

- Potential risks were identified for workers for irritation and corrosion to the eyes and skin for handling glucaric acid in solution based on the SDS. Potential risks for these hazard endpoints were not quantified due to a lack of dose-response for these hazards. Risks would be mitigated if exposures can be controlled by the use of appropriate PPE, including impervious gloves and eye protection.

1.2.2 General Population

- Risks to the general population were not evaluated as no relevant hazard concerns were identified for this PMN.

1.2.3 Consumers

- Risks to consumers were not evaluated as no consumer uses are expected under the intended conditions of use.

1.3 Potentially Useful Information:

1.3.1 Assumptions and Uncertainties

- There are no measured data on the PMN substance itself.
- Health effects are based on analog data and the SDS.

1.3.2 Potentially Useful Information

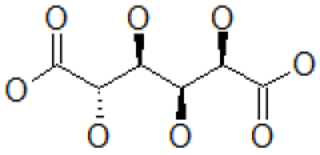
- None identified

[redacted]

2 HUMAN HEALTH HAZARD- PART A

2.1 Chemistry Summary

PMN: P-18-0227	Submitter: [redacted]			Manu.	Import
Max. PV (KG): [redacted]		Binding Option Marked:		X	
MW: 210.14		% < 500		% <1000	CASNO.: 87-73-0

PMN Structure	Prop.	Meas.	Est.
	MP	[redacted]	
	BP		[redacted]
	Pres.		[redacted]
	VP		[redacted]
	S-H2O	[redacted]	[redacted]
	log P		[redacted]

Chemical Name	Analogs:
D-Glucaric acid	[redacted]
Chemical intermediate for [redacted]	[redacted]

Other Names (Synonyms)- D-Saccharic Acid
Molecular Formula- $C_6H_{10}O_8$
Trade Name- KGA50 (product containing the notified substance at 35-60%), KGAP
SMILES- OC(=O)C(O)C(O)C(O)C(O)C(=O)O

Marketed as two forms- [redacted]

Functional Use- 1) chemical intermediate for [redacted])
[redacted])
2) [redacted]

[redacted]

Other Physicochemical data- pKa (dissociation constant) = 3.01 (via OECD QSAR toolbox)

2.1 SAR Summary

2.1.1 Absorption

Absorption of the neat solid crystalline powder material is expected to be poor through the skin and good through the lung and G.I.

When in aqueous solution, absorption is expected to be moderate through the skin and good through the lung and G.I.

Absorption is based on physical/chemical property considerations of molecular size, water solubility, and estimated hydrophilicity and on guidelines in the Qualitative Absorption Approaches for Assessment of PMN Chemicals.

2.1.2 Metabolism

Highly biodegradable to shorter chain sugars.
In equilibrium with glucaric acid lactone form.

2.1.3 Structural Alerts: Parent Compound and/or Metabolites

SA: Parent and/or Metabolites:
No structural alerts identified for the parent chemical (D-glucaric acid). There are reactive structural alerts and/or concerns for some lactones (ex. beta-lactones and alpha-methylene gamma-lactones) yet there are no concerns identified for the gamma-glucaric acid lactones that may exist in equilibrium aqueous solution for protein binding via a ring opening nucleophilic SN2 reaction.

The potential concern for lactone reactivity here is mitigated due to the structural composition of the PMN substance and due to the diacid-favored equilibrium shift during the intended use and application of the PMN substance.

Hazard(s) Associated: N/A
% of Structure:

2.1.4 Chemical Categories

New Chemicals Category: None Identified

New Chemicals Category Health Concerns: N/A

Category Testing Strategy:

[redacted]

Other Chemicals Category: (e.g., HPV, OECD SIDS)

Other Chemicals Category Health Concerns:

2.2 Toxicity Data Summary

2.2.1 **PMN Data** (study summary, reference or source, POD)

- No data submitted with the PMN
- **Calcium D-glucarate, the calcium salt of D-glucaric acid;**
    - An Alternative Medicine Review of Calcium D-glucarate identifies medical uses, health benefits, recommended doses and cites feeding studies to rats and mice. The Alternative Medicine Review can be found at http://www.altmedrev.com/archive/publications/7/4/336.pdf . The reference for the feeding studies is https://www.ncbi.nlm.nih.gov/pubmed/6930942.
      EPA reviewed the report, but not the underlying data.

    - The results of a preliminary human study with calcium glucarate supplementation is documented here: https://www.ncbi.nlm.nih.gov/pubmed/15136472
      EPA reviewed the report, but not the underlying data.

From the Alternative Medicine Review:
Introduction
Calcium-D-glucarate is the calcium salt of D-glucaric acid, a substance produced naturally in small amounts by mammals, including humans. Glucaric acid is also found in many fruits and vegetables with the highest concentrations to be found in oranges, apples, grapefruit, and cruciferous vegetables. 1 Oral supplementation of calcium-D-glucarate has been shown to inhibit beta-glucuronidase, an enzyme produced by colonic microflora and involved in Phase II liver detoxification. Elevated beta-glucuronidase activity is associated with an increased risk for various cancers, particularly hormone-dependent cancers such as breast, prostate, and colon cancers.2 Other potential clinical applications of oral calcium-D-glucarate include regulation of estrogen metabolism and as a lipid-lowering agent.

- **D-glucaric acid (saccharic acid, CAS 87-73-0);**
    - PubChem lists warnings on D-glucaric acid for severe skin burns and damage based on info in ECHA Infocard. PubChem also has other info, such as biochemistry.
      https://pubchem.ncbi.nlm.nih.gov/compound/Saccharic_acid#section=Safety-and-Hazards

[redacted]

9 Safety and Hazards

9.1 Hazards Identification

9.1.1 GHS Classification

Signal: Danger
GHS Hazard Statements
The GHS information provided by 1 company from 1 notification to the ECHA C&L Inventory.

H314 (100%): Causes severe skin burns and eye damage [Danger Skin corrosion/irritation]
H318 (100%): Causes serious eye damage [Danger Serious eye damage/eye irritation]

Precautionary Statement Codes
P260, P264, P280, P301+P330+P331, P303+P361+P353, P304+P340, P305+P351+P338, P310, P321, P363, P405, and P501
(The corresponding statement to each P-code can be found here.)

from European Chemicals Agency (ECHA)

2.2.2 **Analog/Metabolite Data** (analog, structure, study summary, reference or source, POD)

- **tartaric acid (CAS 87-69-4 and CAS 526-83-0).**
  - PubChem has toxicity information on tartaric acid (CAS 87-69- 4 and CAS 526-83-0) https://pubchem.ncbi.nlm.nih.gov/compound/L-tartaric_acid#section=Ingestion-Symptoms
    EPA reviewed the information but not underlying data.

12.1.6 Toxicity Summary

Toxicity

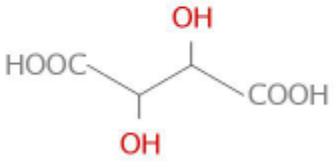
Routes of Entry: Inhalation. Ingestion. Toxicity to Animals: Lowest Published Lethal Dose: LDL [Rat - Route: oral; Dose: 7500 mg/kg LDL [Rabbit] - Route: Oral; Dose: 5000 mg/kg LDL [Dog] - Rout: Oral; Dose: 5000 mg/kg Lethal Dose/Conc 50% kill: LD50 [Mouse] - Route: Intravenous; Dose: 485 mg/kg Other Toxic Effects on Humans: Acute Potential Health Effects: Skin: Causes skin irritation Eyes: Causes eye irritation Inhalation: Causes respiratory tract irritation Ingestion: Causes gastrointestinal tract irritation with nausea, vomiting and diarrhea. May affect kidneys (kidney damage), blood, and behavior (convulsions, somnolence), and respiration. Chronic Potential Health Effects: Ingestion: Repeated or prolonged ingestion may cause lesions of the mouth, gastric ulcers, gastrointestinal hyperacidity, and symptoms similar to those of metal fume fever - flu-like condition with fever, chills, sweats, nausea, vomiting, muscle aches, pains, and weakness. Skin: Repeated or prolonged skin contact may cause skin ulcerations or lesions.

from DrugBank

  - There is an ECHA registration dossier with tox data for CAS 87-69-4, tartaric acid https://echa.europa.eu/cs/registration-dossier/-/registered-dossier/15126
    EPA reviewed the ECHA dossier but did not have access to the studies and relied on ECHA dossier summaries.

[redacted]

Identification



Display Name:	(+)-tartaric acid
EC Number:	201-766-0
EC Name:	(+)-tartaric acid
CAS Number:	87-69-4
Molecular formula:	C4H6O6
IUPAC Name:	(2R,3R)-2,3-dihydroxybutanedioic acid

Toxicokinetics:

Applicant's summary and conclusion

Conclusions:	Interpretation of results (migrated information): bioaccumulation potential cannot be judged based on study results Oral dose of L (+) - tartrate was extensively absorbed and that a part was completely metabolized to CO2 after oral or parenteral administration
Executive summary:	Tartaric acid was not only metabolished by the gut flora and systemic metabolism occurs. Comparison of results obtained after oral or i.v. doses indicates that an oral dose of L (+) - tartrate was extensively absorbed and that a part was completely metaboliszed to CO2 after oral or parenteral administration

ECHA Summary Results (original studies not obtained/reviewed by EPA)
Acute toxicity oral: On the basis of the obtained results, interpreted according to OECD number 423 December 17th 2001, the test product "tartaric acid" has a LD50 > 2000 mg/kg bw and is included into the Acute Toxicity category 5 according to the GHS classification system.

Acute toxicity dermal: On the basis of obtained results, according to Official Journal of the European Union 1272/2008 (CLP) dated December 16th 2008 and OECD Guideline 402 of February 24th 1987, the test substance "tartaric acid" has a LD50 > 2000 mg/kg bw and can be considered non-classified.

Skin Irritation: On the basis of the results, interpreted according to Official Journal of the European Union 1272/2008 (CLP) dated December 16th 2008 and OECD number 404 April 24th 2002, the test substance 'tartaric acid' must be considered not irritant for the skin.

Eye Irritation: According to the evaluation criteria the test item Tartaric Acid is classified as very severe eye irritant. OECD guideline 437 (Bovine Corneal Opacity and Permeability test method for identifying ocular corrosives and severe irritants)

Sensitization: The EC3 value (derived by linear interpolation) could not be calculated as the stimulation indices of all concentrations were below 3.

The results of radioactivity determination were supported by the means of the ear thickness per group, which showed no significant difference compared to the negative control.

[redacted]

Consequently, according to OECD 429 [3] and the criteria given in Annex I of Regulation (EC) 1272/2008 [6], the test item Tartaric Acid, as described in this report is expected to have no sensitising properties and therefore, should not be regarded as a dermal sensitiser.

Repeated Dose Oral: Analog read across Monosodium L(+)-tartrate was fed to rats in their diet for a total of two years at levels of 25600, 42240, 60160 and 76800 ppm. There were no adverse clinical signs and the investigation of the animals' eyes, blood and urine did not reveal any reaction to treatment, nor were changes related to treatment seen in the macroscopic pathology or organ weights of rats killed after 104 weeks. Histological examination of the tissues did not show evidence of toxicity or tumour induction that could be attributed to treatment with monosodium L(+)-tartrate. Only the survival of rats receiving 42240, 60160 or 76800 ppm was superior to that of the controls and probably correlated with the lower food intake of these groups and the resultant reduced bodyweight gain.

Genetic Toxicity: Salmonella/microsome tests (Ames tests) were carried out on D(-)-tartaric acid here. And no significant increases in the number of revertant colonies were detected in any S. typhimurium strains at 10 mg/plate dose with and without metabolic activation.

The Dominant Lethal Test is an accurate and sensitive measure of the amount and type of fetal wastage which may occur following administration of a potential mutagen. In this test acute and subacute administration were carried out in rats, and the results can not be concluded that FDA 71 -55 is a potential mutagen.

Developmental Toxicity: OECD Guideline 414 (Prenatal Developmental Toxicity Study)The administration of up to 274 mg/kg bw of tartaric acid to pregnant mice for 10 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls.

SCIL: Used in dishwasher detergents and acts as a chelating agent that ties up hard water calcium and magnesium ions to make detergents more efficient. Replacement for phosphates in most detergents. (sodium glucarate 1362053-75-5 is on SCIL with full green circle.

No identified acute or repeated dose toxicity concerns based on PMN and analog data.
No concern for sensitization.

2.3 Data Synthesis

2.3.1 Consensus Hazards and Basis (hazard, basis – SAR, Metabolite, PMN or Analog Data, etc.)

The hazard assessment is based on data on the chemical structure of the PMN, the physical chemical properties (molecular size, water solubility, and estimated hydrophilicity), limited information on D-glucaric acid and on the analog tartaric acid (CAS RN 87-69-4 and CASRN 526-83-0). There are no identified structural alerts or available QSAR data.

Absorption of the neat solid crystalline powder material is expected to be poor through the skin and good through the lung and gastrointestinal (GI) tract. When in aqueous solution, absorption is expected to be moderate through the skin and good through the lung and G.I.

There is concern for irritation of the eye, skin and lung, based on the PMN and analog data. There is concern for corrosivity for handling glucaric acid in solution. There are no additional identified hazards associated with acute or repeated dosing based on PMN and analog data. The lowest identified effect

level was the NOAEL of 274 mg/kg bw/day based on no effects at highest dose tested for tartaric acid in an OECD Guideline 414 study (Prenatal Developmental Toxicity Study). **As no systemic hazard concerns were identified for this PMN and no effects were identified in the available repeated dose studies, a quantitative human health risk assessment is not warranted.**

2.3.2 POD for

POD type: There are no points of departures for sensitization and irritation concerns for this PMN
POD Value: N/A
POD Chemical: N/A
POD Route: N/A
POD Hazard Endpoint: N/A
POD Basis: N/A
POD Benchmark MOE: N/A
Reference: N/A

2.3.3 Hazards for Qualitative Assessment

Irritation and corrosivity (dermal and eye, when in solution), and irritation to lungs.

[redacted]

3 HUMAN HEALTH RISK (PART B)

3.1 USES and EXPOSURES

3.1.1 Uses

Chemical intermediate for [redacted]

3.1.2 Worker Exposure

3.1.2.1 Inhalation

Manufacturing

Exposure to Particulate (non-volatile) (Class I)
Upper Bound Potential Dose Rate: [redacted]

Use 1: [redacted]
Exposure to Particulate (non-volatile) (Class I)
Worst Case Potential Dose Rate: [redacted]

Processing 2: [redacted]
Air releases are **negligible** (VP < 0.001 torr) and generation of mists/aerosols is not expected during this operation

Use 2: [redacted]
Air releases are **negligible** (VP < 0.001 torr) and generation of mists/aerosols is not expected during this operation.

3.1.2.2 Dermal

Manufacturing

Exposure to Liquid at [redacted]
High End Potential Dose Rate: [redacted]

Exposure to Solid at [redacted]
High End Potential Dose Rate: [redacted]

Use 1: Intermediate [redacted]
Exposure to Solid at [redacted]
High End Potential Dose Rate: [redacted]

Processing 2: [redacted]
Exposure to Liquid at 50.00% concentration
High End Potential Dose Rate: [redacted]

Use 2: [redacted]
Exposure to Liquid at [redacted]
High End Potential Dose Rate: [redacted]

[redacted]

3.1.3 General Population Exposure:

Exposures to the general population were not estimated d as no systemic hazard concerns were identified for this PMN.

3.1.4 Consumer Exposure

Exposures to consumers were not estimated due to no expected consumer use under the stated conditions of use.

3.2 RISK CALCULATIONS

3.2.1 Worker Calculations

Potential risks were identified for workers for irritation and corrosion to the eyes and skin for handling glucaric acid in solution (all scenarios) based on information in the SDS and analog data. Potential risks for these hazard endpoints were not quantified due to a lack of dose-response for these hazards.

3.2.2 General Population Calculations

Risks to the general population were not evaluated as no relevant hazard concerns were identified for this PMN.

3.2.3 Consumer Calculations

Risks to consumers were not evaluated as no consumer uses are expected under the intended conditions of use.